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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/825,568	04/14/2004	Brian T. Chait	0112602.00152 US3	9114

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WILMERHALE/BOSTON
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EXAMINER	
AUDET, MAURY A	

ART UNIT	PAPER NUMBER
1654	

NOTIFICATION DATE	DELIVERY MODE
01/12/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/825,568	CHAIT ET AL.	
	Examiner	Art Unit	
	MAURY AUDET	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *526-585* is/are pending in the application.

4a) Of the above claim(s) *529,532-535,537,539-542,552,553 and 555-576* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *526-528,530,531,536,538,543-551,554 and 577-585* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

As noted previously, the present application has been transferred from former Examiner Khana to the present Examiner. This Examiner acknowledges the parent application patent number 6,824,981. Notwithstanding the '981 application and prosecution/examination thereto, Applicant is reminded that each application is examined on it's own merits. (Another application S.N. 11/344,801, US Publication 20070207555, has also been filed, but to specific reporter peptides that do not overlap the presently elected SEQ ID NO: 1).

Due to the new grounds of rejection, the present application is sent Non-Final.

Election/Restrictions

As noted previously, Applicant's election with traverse of Group I, claims 526-554 and 577-586, as drawn to the peptide SEQ ID NO: 1 (Cys Gly Gly Gly Gly Asp Pro Gly Gly Gly Gly Arg) in the reply filed on 7/23/07 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to search all the peptides claimed. This is not found persuasive because the peptides are independent and distinct and searching more than one not containing at least an overlapping core would constitute an undue search burden (each peptide sequence requires a search of 5-7 peptide databases and examination of the results of each database for each peptide search).

As the previous Examiner had required:

In Groups I-II, the species of SEQ ID NO: 1, 24-26 and isotopic variants thereof are independent or distinct because they are drawn to varying lengths having different

sequences and chemical structures. It would be an undue burden to examine all the species in one application particularly with respect to their being non-obvious variants.

Applicant is required under 35 U.S.C. 121 to elect a single Group, within that Group a single SEQ ID NO., and elect a completely defined species of that SEQ ID NO. represented by the positions of the isotopes or chemical reactive groups, even though this requirement is traversed.

Notwithstanding the above, this Examiner was willing to search the elected peptide of SEQ ID NO: 1 and any other peptides bearing the same overlapping core (as Applicant indicated, 4 heavy glycines). HOWEVER, of the 18 peptides Applicant has described in the sequence list/specification, no other peptides were found to contain an overlapping core with that of elected SEQ ID NO: 1. Thus, the only peptide that could be searched commensurate in scope with the elected species, without an undue search burden, was that of the elected peptide of SEQ ID NO: 1.

Claims 555-576 are pending. Claims 529,532-535,537,539-542,552,553 and 555-576 are withdrawn. Claims 526-528,530,531,536,538,543-551,554 and 577-585 are examined on the merits as drawn to SEQ ID NO: 1.

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejections - 35 USC § 112 1st Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 526-528,530,531,536,538,543-551,554 and 577-585 are under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, other than the fully described elected SEQ ID NO: 1.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); In re Gostelli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966." Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

"A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers,* 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe,* 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.,* 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the . sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP§ 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli,* the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli,* 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art,* (2) *partial structure,* (3) *physical and/or chemical properties,* (4) *functional characteristics alone or coupled with a known or disclosed*

correlation between structure and function, and the (5) *method of making the claimed invention.* Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

In the instant case, the claims are drawn to a peptide structure comprising Asp-Pro peptide of about10-35 amino acids that is asserted to function as "reporter signal peptides", e.g. capable of eliciting some non-specific signal (that, as an aside, must be also be specific, substantial, and credible to pass the lower threshold utility requirement under 35 USC 101). A search of the present application for "reporter signal" and "Asp-Pro" produced the following description related to 'function", which is not currently deemed to render a fishing expedition of may be on either side of Asp-Pro, very descriptive as to what amino acids must be added to Asp-Pro, in order to obtain the proper "functionality" – in other words, it is unclear what the structure of these peptides are supposed to be in end-product stage in order to carry out the "function" prong of the written desription test as to what peptide Applicant had "possession" of at the time of the invention:

> [0138] As an example of reporter signal protein calibration, a protein sample of interest can be digested with a serine protease, preferably trypsin. The digest generates a complex mixture of protein fragments. Among these protein fragments, there will exist a subset (approximately one protein fragment among every 400) that contains the dipeptide Asp-Pro. This dipeptide sequence is uniquely sensitive to fragmentation during mass spectrometry, an thus produces a high yield of ions in fragmentation mode. Since the human proteome consists of at least 2,000,000 distinct tryptic peptides, the number of protein fragments containing the Asp-Pro sequence is of the order of 5,000. Since some of these may exist as phosphopeptides or other modified forms, the number may be even higher. This number is sufficiently high to permit the

selection of a subset (perhaps 50 to 100 or so) of fragmentable protein fragments that is suitable for generating a highly informative protein signature. Peptides that contain the Asp-Pro dipeptide sequence, peptides that contain amino acids that are modified by phosphorylation inside the cell, or peptides that contain an internal methionine are particularly preferred for use in reporter signal calibration. Alternatively, tryptic peptides terminating in arginine may be modified by reaction with acetylacetone (pentane-2,4-dione) to increase the frequency of fragment ions (Dikler et al., J Mass Spectrom 32:1337-49 (1997)). Selection of the subsets of protein fragments can be performed using bioinformatics in order to maximize the information content of the protein signatures.

Detail Description Paragraph - DETX (61):

[0139] For this form of reporter signal protein calibration, the protein digest can be mixed with a specially designed set of reporter signal calibrators, and then is analyzed using tandem mass spectrometry. In the case of a tandem in space instrument (for example, Q-Tof.TM. from Micromass), using first quadrupole settings for single-ion filtering (defined by the molecular mass of each unique fragment, which can be obtained from sequence data), followed by a collision stage for ion fragmentation, and finally TOF spectrometry of the peptide fragments (generated by cleavage at fragile bonds, such as Asp-Pro, bonds involving a phosphorylated amino acid, or bonds adjacent to an oxidized amino-acid such as methionine sulfoxide, Smith et al., Free Radic Res. 26:103-11 (1997)) that arise from the original single-ion. In the second stage, signal to noise of the TOF measurement is much larger than in a conventional MS experiment. In general, one reporter signal calibrator can be used for each protein fragment in the sample that will be used to make up the protein signature (such protein fragments are referred to as signature protein fragments), and each is designed to fragment in an easily detectable pattern of masses, distinct from the fragment masses of the unfragmented signature protein fragments. The quadrupole filtering settings are then varied in sequence over a range of values (fifty, for example), corresponding to the masses of each of the protein fragments previously chosen to comprise the protein signature (that is, the signature protein fragments). At each filtered mass setting, there will be two types of signals detectable by TOF after fragmentation, one set derived from the tryptic peptide (that is, the original protein fragment), and another set corresponding to the reporter signal calibrator. The reporter signal calibrator permits one to calculate relative abundance for each of the signature protein fragments. These relative abundance ratios, determined for a given sample, constitute the protein signature. The detection limit of the tandem mass spectrometer in MS/MS mode, is remarkably good, perhaps of the order of 500 molecules of peptide. This level of detection is approximately 1,000 times better than that for MALDI-TOF mass spectrometry, and should permit the generation of protein signatures from single cells.

[0569] As an example of reporter signal protein calibration, a protein sample of interest can be digested with a serine protease, preferably trypsin. The digest generates a complex mixture of protein fragments. Among these protein fragments, there will exist a subset (approximately one protein fragment among every 400) that contains the dipeptide Asp-Pro. This dipeptide sequence is uniquely sensitive to fragmentation during mass spectrometry, an thus produces a high yield of ions in fragmentation mode. Since the human proteome consists of at least 2,000,000 distinct tryptic peptides, the number of protein fragments containing the Asp-Pro sequence is of the order of 5,000. Since some of these may exist as phosphopeptides or other modified forms, the number may be even higher. This number is sufficiently high to permit the selection of a subset (perhaps 50 to 100 or so) of fragmentable protein fragments that is suitable for generating a highly informative protein signature. Peptides that contain the Asp-Pro dipeptide sequence, peptides that contain amino acids that are modified by phosphorylation inside the cell, or peptides that contain an internal methionine are particularly preferred for use in reporter signal calibration. Alternatively, tryptic peptides terminating in arginine may be modified by reaction with acetylacetone (pentane-2,4-dione) to increase the frequency of fragment ions (Dikler et al., J Mass Spectrom 32:1337-49 (1997)). Selection of the subsets of protein fragments can be performed using bioinformatics in order to maximize the information content of the protein signatures.

[0570] For this form of reporter signal calibration, the protein digest can be mixed with a specially designed set of reporter signal calibrators, and then can be analyzed using tandem mass spectrometry. In the case of a tandem in space instrument (for example, Q-Tof.TM. from Micromass), using first quadrupole settings for single-ion filtering (defined by the molecular mass of each unique fragment, which can be obtained from sequence data), followed by a collision stage for ion fragmentation, and finally TOF spectrometry of the peptide fragments (generated by cleavage at fragile bonds, such as Asp-Pro, bonds involving a phosphorylated amino-acid, or bonds adjacent to an oxidized amino-acid such as methionine sulfoxide, Smith et al., Free Radic Res. 26:103-11 (1997)) that arise from the original single-ion. In the second stage, signal to noise of the TOF measurement is much larger than in a conventional MS experiment. In general, one reporter signal calibrator can be used for each protein fragment in the sample that will be used to make up the protein signature (such protein fragments are referred to as signature protein fragments), and each is designed to fragment in an easily detectable pattern of masses, distinct from the fragment masses of the unfragmented signature protein fragments. The quadrupole filtering settings are then varied in sequence over a range of values (fifty, for example), corresponding to the masses of each of the protein fragments previously chosen to comprise the protein signature (that

> is, the signature protein fragments). At each filtered mass setting, there will be two types of signals detectable by TOF after fragmentation, one set derived from the tryptic peptide (that is, the original protein fragment), and another set corresponding to the reporter signal calibrator. The reporter signal calibrator permits one to calculate relative abundance for each of the signature protein fragments. These relative abundance ratios, determined for a given sample, constitute the protein signature. The detection limit of the tandem mass spectrometer in MS/MS mode, is remarkably good, perhaps of the order of 500 molecules of peptide. This level of detection is approximately 1,000 times better than that for MALDI-TOF mass spectrometry, and should permit the generation of protein signatures from single cells.

(1) Level of skill and knowledge in the art: The level of skill or knowledge in the art is high, being that of a researcher or medical/veterinary practitioner with post-graduate training and experience in the methods of peptide purification and analysis.

(2) Partial structure: Applicant has disclosed a dipeptide of Asp-Pro, and no more, other than the elected fully described peptide.

(3) Physical and or chemical properties: the physical properties claimed are that the peptide must function as a "reporter signal" for some signal-related benefit.

(4) Functional characteristics: the functional characteristic that of a "signal" reporter, for some desired signal.

(5) Method of making the claimed invention: Solid phase synthesis or by cultivating cells that are capable of biosynthesis of the peptide, traditional methods of peptide synthesis.

As stated *supra,* the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. The present claims are broadly generic to all possible polypeptides encompassed by the claims. The possible variations are enormous to any class of variable polypeptides. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional

characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of the polypeptides partially defined by SEQ ID NO:1 beyond those disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of practical signal use of any peptides of SEQ ID NO:8 other than the full SEQ ID NO: 1, nor does it provide any rationale that relates any part or parts of the structure to the antimicrobial function.

While having written description of the full elected SEQ ID NO: 1 amino acid sequence identified in the specification tables and/or examples, the specification is devoid of any examples or structure/activity relationships that qualify for the functional characteristics claimed.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder,* 736, F.2d 1516, 1521,222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants, hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly it is deemed that the specification fails to provide adequate written description for the genus of the claims and, does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Allowable Subject Matter

As indicated previously, the prior art of record does not reasonably teach or render obvious a peptide selected from the group consisting of the elected species of SEQ ID NO: 1, having 4 heavy chain glycine; or set or kit thereto. Were claims 526-554 and 577-585 amended thereto (reporter peptide consisting of SEQ ID NO: 1), the claims would likely receive favorable consideration.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MAURY AUDET whose telephone number is (571)272-0960. The examiner can normally be reached on M-Th. 7AM-5:30PM (10 Hrs.).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). MAA, 1/2/09

/Maury Audet/
Examiner, Art Unit 1654